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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/619,539 | 07/16/2003 | H. William Bosch | 029318-0961 | 6324 |

31049 7590 09/08/2009

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| EXAMINER | |
|---|---|
| TRAN, SUSAN T | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1615 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 09/08/2009 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/619,539 | BOSCH ET AL. | |
| | Examiner | Art Unit | |
| | S. Tran | 1615 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-3,5-35,37,39,41,43-52,54-82 and 84-123* is/are pending in the application.

4a) Of the above claim(s) *46-52,54-82 and 84-123* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-35,37,39,41 and 43-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

In view of the Appeal Brief filed on 05/05/09, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

/MP WOODWARD/

Supervisory Patent Examiner, Art Unit 1615

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 2 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The present specification discloses that only certain nanoparticulate active agents from needle-like crystals in a liquid dosage composition (page 21, lines 1-2). The specification further disclosed that the active agent of the present invention is of a type that forms undesirable crystals during storage and/or heat sterilization (page 21, lines 5-7). The specification, however, does not show if all of the active agents disclosed in pages 21-23 possess the claimed limitation, which form undesirable crystals during storage and/or heat sterilization. Absent a clear indication from the present specification, a burdensome amount of research would be required by one of ordinary skill in the art determine the storage condition of the unlimited number of active agents disclosed in the present specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 is being rejected for failing to further limit the subject matter of claim 1. While claim 15 requires that the composition is a tablet, a fast melt, or a lyophilized formulation, claim 1 recites that the composition is a liquid dosage form.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5, 6, 8-19, 21-24, 27-29, 32-35, 37, 39, 41 and 43-45 are rejected under 35 U.S.C. 102(b) as being anticipated by Liversidge et al. US 5,302,401 (Liversidge '401).

Liversidge '401 teaches a suspension composition comprising of nanoparticles having a surface modifier adsorbed on the surface thereof, and a cryoprotectant associated with (abstract). Surface modifier includes the claimed surface stabilizer. See column 2. Combination of two or more surface modifier is taught in column 2, lines 65-68. The amount of surface modifier ranges from about 0.1% to about 90% by weight based on the total combined weight of the drug substance add the surface modifier (column 3, lines 31-35). Cryoprotectant includes mannitol and glycerol (column 5, lines 27-30). Cryoprotectant is used in an amount of 0.5% to 90% based on the total weight of the nanoparticulate suspension (column 5, lines 37-39). Liversidge '401 further teaches the viscosity of the suspension is less than about 1000 centipoise (column 3,

lines 36-38). The average particle size of the nanoparticle is less than 400 nm (column 5, lines 1-14). The active agent has particle size of less than about 400 nm (column 5, lines 45-48). Liversidge '401 further teaches that liquid medium such as water can be used as the pharmaceutically acceptable carrier (column 5, lines 53-55).

It is of note that Liversidge '401 does not explicitly teach the claimed properties such as: the amount of active agent per ml is equal to or greater than the amount of the active agent per ml of a standard conventional non-nanoparticulate liquid dosage composition of the same active agent; and the pharmacokinetic, e.g., $T_{max}$ and $C_{max}$ of the composition.

However, such properties are inherent because Liversidge '401 teaches the same nanoparticulate composition comprising the same surface stabilizer and cryoprotectant (osmotically active crystal growth inhibitor) in the claimed amounts, which exhibits the property desired by applicant, namely, a nanoparticulate composition that is stable and have reduced or no particle size growth (column 1, lines 28-34). This is also because when the claimed and prior art products are identical or substantially identical in structure or composition, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977).

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 5-24, 26-31, 35, 37, 39, 41 and 43-45 are rejected under 35 U.S.C. 102(e) as being anticipated by Kipp et al. US 2003/0077329.

Kipp discloses a stable suspension of poorly water soluble pharmaceutical agent. The suspension comprises nanoparticles of a pharmaceutical active agent having average diameter less than about 200 nm suspended in an aqueous matrix, and one or more excipients (abstract; and paragraphs 0042, 0050, 0078 and 0084). Excipients include: 1) two or more surface modifiers (paragraphs 0063-0068); 2) crystal growth modifier (paragraph 0070); 3) cryoprotectant compounds (paragraph 0071); and osmotic agent such as mannitol, glycerol, and sodium chloride (paragraph 0073). Excipients are used in an amount ranges from 0.001-20% (paragraph 0075). The suspension is suitable for a wide variety of administration including parenteral (abstract; and paragraph 0043).

It is noted that Kipp does not explicitly teach the claimed properties such as: the amount of active agent per ml is equal to or greater than the amount of the active agent per ml of a standard conventional non-nanoparticulate liquid dosage composition of the same active agent; and the pharmacokinetic, e.g., $T_{max}$ and $C_{max}$ of the composition.

However, such properties are inherent because Kipp teaches the same nanoparticulate composition comprising the same surface stabilizer and osmotic agent in the claimed amounts, which exhibits the property desired by applicant, namely, a

stable nanoparticulate composition suitable for poorly water soluble active agent (paragraph 0004). This is also because when the claimed and prior art products are identical or substantially identical in structure or composition, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977).

***Claim Rejections - 35 USC § 103***

Claims 1-3, 5-24, 27-29, 32-35, 37, 39, 41 and 43-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liversidge '041, in view of Brockbank et al. WO 01/78505 A1 or Kipp et al. US 2003/0077329.

Liversidge is relied upon for the reason stated above. Liversidge does not explicitly teach cryoprotectant compound includes sodium chloride, and in the case that applicant selects other crystal growth inhibitor from the Markush group recites in claim 1. Brockbank teaches cryoprotectant compound includes lactose, mannitol, mannose, glycose, xylitol, sorbitol, magnesium chloride, propylene glycol, glycerol, or sodium chloride (paragraph 0024).

Kipp discloses a stable suspension of poorly water soluble pharmaceutical agent. The suspension comprises nanoparticles of a pharmaceutical active agent having average diameter less than about 200 nm suspended in an aqueous matrix, and one or more excipients (abstract; and paragraphs 0042, 0050, 0078 and 0084). Excipients include: 1) two or more surface modifiers (paragraphs 0063-0068); 2) crystal growth modifier (paragraph 0070); 3) cryoprotectant compounds (paragraph 0071); and

osmotic agent such as mannitol, glycerol, and sodium chloride (paragraph 0073). Excipients are used in an amount ranges from 0.001-20% (paragraph 0075).

Thus, it would have been obvious to one of ordinary skill in the art to, by routine experimentation optimize the nanoparticle composition of Liversidge '401 to include sodium chloride in view of the teachings of Brockbank or Kipp. This is because Brockbank teaches that lactose, mannitol, mannose, glycose, xylitol, sorbitol, magnesium chloride, propylene glycol, glycerol, and sodium chloride are well known cryoprotectant compounds, because Kipp teaches a stable nanoparticulate composition with the use of the claimed osmotic agent such as mannitol, glycerol, or sodium chloride, and because Liversidge '401 teaches the desirability for using agents such as mannitol, glycerol, and the like.

Claims 25-35, 37, 39, 41 and 43-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liversidge '401, in view of Liversidge US 2005/0004049 (Liversidge '049).

Liversidge '401 is relied upon for the reason stated above. The reference does not teach the claimed specific active agent suitable in a bioadhesive composition.

Liversidge '049 teaches a nanoparticulate composition comprising surface modifier, and a drug having solubility of less than about 30 mg/ml (abstract; and paragraph 0045). Drug including analgesic, NSAID and vitamins are discloses in paragraphs 0109-0113). The nanoparticulate composition is processed into a liquid dosage for bioadhesive composition (paragraphs 0081-0089). Liversidge further

teaches the claimed viscosity, $C_{max}$, $T_{max}$, and bioequivalency (paragraphs 0090-0105). Thus, it would have been obvious to one of ordinary skill in the art to modify the nanoparticulate composition of Liversidge '401 to include active agents in view of the teachings of Liversidge '049 to obtain a useful bioadhesive composition of the present invention. This is because Liversidge '049 teaches that the claimed active agents in nanoparticulate dosage form is known in the art, and because Liversidge '401 teaches a stable nanoparticulate composition suitable for a wide variety of active agents.

***Response to Arguments***

Applicant's arguments filed 05/05/09 have been considered but are moot in view of the new ground(s) of rejection.

***Correspondence***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to S. Tran whose telephone number is (571) 272-0606. The examiner can normally be reached on M-F 8:00 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. Tran/
Primary Examiner, Art Unit 1615